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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	
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07/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,015	SHIRASAKI ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-11 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6 and 8-11* is/are rejected.

7)☒ Claim(s) *7 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/06, 8/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The election of species requirement mailed 3/4/2008 is vacated. The compounds of amended formula (I) are free of the prior art. Claims 1, 3, 6-11 and 20 are pending.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3, 6 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: linkage between the pyridyl group in R^1 and the C_{1-3} alkyl. It is not clear from the formula as recited in claim 1 what the structure R^1 is.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating retinal ischemia reperfusion injury, does not reasonably provide enablement for the treatment and/or prophylaxis of all other calpain related

diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and are as follows:

The Nature of the Invention

The invention is drawn to alpha-ketoamide derivatives of formula (I) which are prophylactic and/or therapeutic agents for diseases related to calpain.

The breadth of the claims

Diseases related to calpain include, but are not limited to, ischemic disease, immunologic disease, multiple sclerosis, Alzheimer's disease, osteoporosis, diseases caused by brain tissue damage, cataract, glaucoma, retinochoroiditis disease, diabetic retinopathy, retinal vein occlusion, macular degeneration, retinitis pigmentosa, hypertensive retinopathy, retinal detachment, posterior eyeball complications due to photocoagulation, macular edema, retinal detachment, optic neuritis, visual field defect, light sense defect, dyschromatopsia, and diseases involving neovascularization. Claim 11 limits the calpain diseases to ischemic disease, immunologic disease, multiple sclerosis, Alzheimer's disease, osteoporosis, diseases caused by brain tissue damage, cataract, glaucoma, retinal disease, retinochoroiditis, posterior eyeball complications due to photocoagulation and a disease involving neovascularization. The specification does not define the genus of immunologic disease, diseases caused by brain tissue damage or diseases involving neovascularization.

The State of the Prior Art and its Predictability or Unpredictability

Carragher (*Curr. Pharm. Des.*, 2006, 12, 615-38) writes: "The calpains represent a well-conserved family of calcium-dependent cysteine proteases. They consist of several ubiquitous and tissue specific isoforms and exhibit broad substrate specificity influencing many aspects of cell physiology including migration, proliferation and apoptosis. Calpain activity *in vivo* is tightly regulated by its natural endogenous inhibitor calpastatin. Calpastatin specifically inhibits calpain and not other cysteine proteases by interaction with several sites on the calpain molecule. Inappropriate regulation of the calpain-calpastatin proteolytic system is associated with several important human pathological disorders including muscular dystrophy, cancer, Alzheimer's disease, neurological injury, ischemia/reperfusion injury, atherosclerosis, diabetes and cataract formation." Calpain inhibitors have been demonstrated to be effective in animal models of Parkinson's, ischemia/reperfusion injury, spinal chord injury, atherosclerosis, cataracts and muscular dystrophy (pp. 624-7). The use of calpain inhibitors to treat Alzheimer's disease or multiple sclerosis has not been reported (p. 625).

Carragher writes: "Recent advances in elucidating the tertiary structures of calpain 2 and its regulatory domain calpain 4, together with identification of new modes of regulating calpain activity provide new opportunities for the design of novel calpain inhibitors." Several classes of inhibitors have been developed, including peptidyl epoxide, aldehyde, and ketoamide inhibitors. The inhibitors of the instant invention are examples of ketoamide inhibitors of calpain (p. 628).

Peptidyl aldehyde inhibitors include leupeptin, MDL-28170, ALLN, SJA-6017 and calpeptin. These compounds are not structurally related to the compounds of the instant invention. They have been shown to have neuroprotective effect in animal models of ischemic injury, diffuse brain injury, cerebral ischemia, Parkinson's, focal ischemic and head injury as

well as to be effective in animal models of restinosis following angioplasty and systemic inflammatory response (p. 628, col. 2, p. 631, col. 1). Peptidyl alpha-ketoamides, such as AK275, which are related to the compounds of the instant invention, have been shown to have neuroprotective effect in focal ischemic brain damage, cerebral artery occlusion and excitotoxic damage (p. 631, col. 1). Non-peptide inhibitor PD150606 has been shown to be effective to treat cataracts and to have neuroprotective effects following excitotoxic injury (p. 631, col. 2).

Carragher writes: "a major limitation to the clinical use of such inhibitors is their lack of specificity among cysteine proteases and other proteolytic enzymes. The development of a new class of calpain inhibitors that interact with domains outside of the catalytic site of calpain may provide greater specificity and therapeutic potential." (abstract)

The Relative Skill of Those in the Art

It is not within the skill of those in the art to use calpain inhibitors to treat or prevent Alzheimer's disease, multiple sclerosis, immunologic disease, osteoporosis, glaucoma, retinal disease, retinochoroiditis, posterior eyeball complications due to photocoagulation or a disease involving neovascularization.

The Amount of Direction or Guidance Presented and the Presence of Working Examples

The specification presents the complete structure of 24 compounds that all exhibit calpain inhibitory activity (compounds 1-24). The specification does not present data regarding the specificity of these compounds with respect to other cysteine proteases or proteolytic enzymes. The specification presents data illustrating that one of the described compounds of formula I, ((1S)-1-((((1S)-1-Benzyl-2,3-dioxo-3-(cyclopropylamino)propyl)amino)carbon- yl)-3-methylbutyl)carbamic acid 5-methoxy-3-oxapentyl ester, is effective in an animal model of

retinal ischemia reperfusion injury (Experimental Example 6). The specification does not provide any guidance on how to use the claimed compounds to treat or prevent immunologic disease, multiple sclerosis, Alzheimer's disease, osteoporosis, diseases caused by brain tissue damage, cataract, glaucoma, retinal disease, retinochoroiditis, posterior eyeball complications due to photocoagulation or a disease involving neovascularization.

The Quantity of Experimentation Necessary

Calpain inhibitors have not been demonstrated to be effective at treating or preventing immunologic disease, multiple sclerosis, Alzheimer's disease, osteoporosis, glaucoma, retinal disease, retinochoroiditis, posterior eyeball complications due to photocoagulation or a disease involving neovascularization. Calpain inhibitors of the same class as the compounds of the instant invention have not been shown to be effective to treat or prevent cataract. In the absence of this validation in the prior art and lack of experimental evidence in the specification that the claimed compounds would be effective to treat and prevent these diseases, the skilled artisan would be burdened with undue experimentation in determining if one of the claimed compounds would be effective at treating or preventing immunologic disease, multiple sclerosis, Alzheimer's disease, osteoporosis, glaucoma, retinal disease, cataracts, retinochoroiditis, posterior eyeball complications due to photocoagulation or a disease involving neovascularization. The skilled artisan would be burdened with testing a broad range of in animal models of each disease. This would be particularly burdensome for immunologic disease and diseases involving neovascularization, which are broad classes of disease lacking a unifying mechanistic cause and target for treatment. The experimentation required represents years of inventive effort.

When the above factors are weighed, it is the examiner's position that with the exception of treating retinal ischemia reperfusion injury, one skilled in the art could not use the compounds of formula I without undue experimentation.

Allowable Subject Matter

7. Claims 7 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

9. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb